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REVIEW

ADIPOSE-DERIVED STEM CELLS AS A REMEDY

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Abstract

Adipobiology of stem cells is reaching enthusiastic proportions in today's regenerative medicine. Current interest in the adipose-derived stem cells (ADSC) stems from their multilineage differentiation potential, and ease of derivation in larger quantities using less invasive methods, compared with other stem cell types. The possible benefits of ADSC-based therapy may be mediated by both cell proliferation/differentiation and paracrine secretion. Adipose tissue's secretome includes adipokines (growth factors, cytokines, chemokines, neuropeptides, hypothalamic hormones/releasing factors), steroid hormones, free fatty acids, prostaglandins, and endocannabinoinds. The present review, focusing on adipose tissue secretory activity, also highlights the possible implication of ADSC in the therapy of various disorders, particularly neurodegenerative diseases, myocardial infarction and stroke as well as gut, liver and skin diseases.

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Key words: adipose tissue, disease, growth factors, secretion, therapy

Introduction

Sixty years after declaring independence, American culture was still heavily influenced by Europe, and Ralf Waldo Emerson forwarded the question "What is the remedy?" in his lecture *The American Scholar* delivered on August 31, 1837 to the Phi Beta Kappa Society at Cambridge, Massachusetts.

Today, human health globally is heavily influenced by cardiovascular and neurodegenerative diseases. And both the society and biomedical scientists are looking for the answer of "What is the remedy?" for these diseases.

The present article highlights the current concepts of adipose-derived stem cells (ADSC), focusing on adipose tissue secretory activity, particularly its paracrine expression. We also outline the possible implication of ADSC in the therapy of various disorders, particularly neurodegenerative diseases, myocardial infarction and stroke as well as gut, liver and skin diseases (1-4).

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Adipose tissue

Although the function and topology of brown adipose tissue have been re-evaluated recently (5), at structural and functional level, white and brown adipose tissue (WAT and BAT, respectively) are traditionally distinguished. WAT is generally partitioned into two main large depots with visceral and subcutaneous location, and many small depots associated with various organs including heart, blood vessels, lymph nodes, eyes as well as parasellar region in the brain and epidural space in the spinal cord. Adipose tissue is a dynamic system, consisting of adipocytes and non-adipocyte cellular elements, including stromal, vascular, nerve and immune cells. These cells may input, process, and output information, a sophisticated biological module resembling brain, particularly hypothalamus (6-8).

At birth, the average-size infant has approximately five billion adipocytes, whereas their total number becomes approximately 80 billion in adults. Adding more than billion fibroblasts, mast cells, lymphocytes, dendritic cells and macrophages makes the whole body adipose tissue a major secretory organ of humans. Adipose tissue modulates whole body metabolism by controlling insulin sensitivity and circulating glucose and fatty acid levels in tissues such as muscle, liver and brain (8-15).

The most momentous challenge that has occurred in the field of adipose tissue research has been the discovery of leptin (from Greek *leptos*, meaning thin), an adipocyte-secreted *Ob* gene-encoded protein, in the end of 1994 (8). This became an acute trigger for the current development of adipobiology, particularly the studies on cell protein secretion in adipose tissue (10,13-15). Hence the current paradigm framed by the two Nobel Prize winners George Palade and Gűnder Blobel regarding the rough endoplasmic reticulum-Golgi complex secretory pathway and the signal hypothesis, respectively, began to be explored in adipose tissue secretion, demonstrating that not only adipocytes but also other adipose cell types express a high secretory phenotype (9-16). For instance, 259 proteins were identified in the cultured human visceral adipose tissue 108 of them being secretory proteins (14), that is, bearing a N-terminal secretion signal peptide. Likewise, another in-depth proteome study on 3T3-L1 adipocytes identified 3 287 proteins (11), at present the largest proteome map of adipocytes.

According to current paradigm, the process of protein secretion is mediated by synthesis, post-translational modification and folding (in the lumen of rough endoplasmic reticulum), sorting and targeting to final destinations such as plasma membrane, nucleus, intracellular organelles, and exocytosis. Briefly, the three major types of secretory proteins are plasmalemmal, intracellular (imported) and exported proteins (13,15,17), the adipokines being an example of the latter class of secretory proteins.

Further, non-rough endoplasmic reticulum-Golgi complex pathways using multivesicular endosome-derived exosomes and plasmalemma-shedding microparticles termed ectosomes are also appreciated in recent studies on adipo-secretion (15,16,18). Hence, both exosomes and ectosomes should also be considered the constituents of adipocyte secretome. Importantly, through endocrine and paracrine pathways these nano-sized structures translocate several membranes, cytosolic and nuclear proteins as well as adiponectin, exosomes being recently coined "adiposomes" (18).

Recently, more than 100 secretory proteins designated adipokines have been identified (9-15). Trayhurn and Wood (10) conceptualized the proteome of adipose tissue as adipokinome, whereas the whole spectrum of adipose secretory products was designated secretome, the latter embodying both proteins (adipokines) and non-proteins such as free fatty acids, steroid hormones (19), endocannabinoids (20) and nitric oxide (21) among others. Using current methodologies of adipoproteomisc (11,14,15), many newcomers are expected to arrive to adipose secretome.

Noteworthy, hypothalamic hormones/releasing factors, neuropeptides and neurotrophic factors are also synthesized and released from adipose tissue (6,7) In effect, all components of adipose secretome may contribute to the regulation of numerous biological functions (appetite, satiety, energy homeostasis, lipid and glucose metabolism, inflammation, immunity, hemostasis, reproduction, aging, learning and cognition) as well as the pathogenesis of cardiometabolic (9,12,13,22,23), gastrointestinal (24-27), neurodegenerative (28-31) and other diseases (9,13).

In brief, the adipose tissue secretome is a potent producer of multiple pleiotropic factors; adipokines with a possible neuroregenerative potential are listed in Table 1. From the perspective of regenerative medicine, such a super-sized secretome may allow transplanted ADSC to exert a strong paracrine activity over the injured tissue. With the use of various bioengineering technologies, this activity may be directed in a tissue- and disease-specific manner.

Adipose-derived stem cells

"In science, as in life, there seem to be three kinds of problems, which we classify as "easy", "difficult", or "impossible". "Easy" problems in science are those in which concept and methodology both appear to be adequate; "difficult" problems are those in which either concept and/or methodology appears to be deficient; "impossible" problems are impossible" –Oscar Hechter wrote in his review "On the action of mammalian hormones" (32). Here, dealing with the adipose secretome in ADSC-based

Table 1. Selected list of "neuroregenerative" adipokines*

Nerve growth factor
Brain-derived neurotrophic factor
Ciliary neurotrophic factor
Glial cell line-derived neurotrophic factor
Vascular endothelial growth factor
Hepatocyte growth factor
Transforming growth factor-β
Granulocyte and macrophage colony stimulating factors
Angiopoietin-1
Insulin-like growth factor
Steroids
Leptin
Neuropeptide Y
Apelin
Metallothionein-I,-II,-III

* For references (6,7,66,68-70).

therapy, the problem may be classified as a difficult, but not impossible problem.

Although the currently popular concept of stem cells can be traced back to the end of the 19th century (reviewed in 33), the potential of ADSC in regenerative medicine has only been appreciated recently (34-45).

Different stem cell populations have been intensively studied in the last decade as a potential source of new cells, for example, cardiomyocytes that can ameliorate the injured myocardium and eventually restore cardiac contractility, neural cells that can rescue injured brain and peripheral nerves.

Stem cells can generally be classified into embryonic and adult form; a variation of the former is so-called induced pluripotent stem (iPS) cells, whereas bone marrow-, umbilical cord- and placenta-derived stem cells as well as ADSC and skin progenitor cells are examples of adult stem cells. For a long time, embryonic stem cells were thought to be the only source of pluripotency, a dogma that has been challenged during the last decade. The derivation of human stem cells from pre-implantation embryos (specifically, from the inner cell mass of the human blastocyst at day 5 or 6 of the early embryo development) raised great expectations for their use in regenerative therapy (33). However, ethical concerns, teratocarcinomas formation upon transplantation and immunological risks became serious limitations at the clinical settings. A feasible alternative option might be provided by auto-transplantation of ADSC or skin-derived precursor cells as easily accessible and ethically acceptable source of stem cells.

The stromal vascular fraction of adipose tissue contains stem cells, T-lymphocytes, anti-inflammatory macrophages, endothelial precursor cells, and preadipocytes. In cell culture conditions, ADSC display an impressive developmental plasticity, including a multilineage differentiation potential; they can differentiate into bone, cartilage, muscle and neuronal cells (46-55). In addition, the ADSC are capable of expressing cholinergic molecules which could be a great news for reducing the burden of Alzheimer's disease (41). Noteworthy, a subset of adipocytes may originate from the neural crest cells (46,47).

Adipose-derived stem cells can be obtained by a less invasive method and in larger quantities compared with bone marrow-derived stem cells and neural stem cells. By liposuction, a common surgical operation, adipose tissue can be harvested in large quantities with minimal side effects from several regions of the body. On average, 100 ml of human adipose tissue yields about 1×10^6 stem cells, or about 5×10^5 stem cells could be obtained from 400 to 600 mg adipose tissue (35,36,43). Also, the flow cytometry analysis has previously reported that ADSC express high levels of stem cell-related antigens (CD13, CD29, CD44, CD105, and CD166) and stem cell-related transcription factors.

Understanding signaling pathways that drive proliferation, transdifferentiation and secretion of ADSC is of great importance for controlling their behavior. Applying efficient cell engineering protocols including encapsulation (in microspheres) of "stem cell growth factors" released into the medium of cultured ADSC may encourage their tissue-specific differentiation potential. Understanding various approaches involving both the transduction and the pharmacology of ADSC could further boost their utility. For instance, (*i*) stem cells transduced with tyrosine hydroxylase and other related genes could function as biological minipumps to enhance the dopaminergic neurotransmission after grafting (56), (*ii*) lovastatin, a cholesterol-lowering drug (57), and berberine, a plant antioxidant (58), both prevent ischemia-induced apoptosis in mesenchymal stem cells, and (*iii*) valproic acid (an anticonvulsant, mood-stabilizing and anticancer drug exerting histone deacetylase inhibitory action) affects neural stem cell proliferation (59) .

ADSC: an "old" remedy?

Recent evidence shows that *Homo obesus* (60, cf. 61,62) is much prone to expressing a surprisingly high number of diseased phenotypes, including those discussed herein (24-31,63-65). Symbolically, if ADSC transplantation may indeed bring therapeutic effects in patients, this might be a science-based rescue of the obese humans suffering from various cardiometabolic and neurodegenerative diseases. Indeed, reminding us of *similia si-*

milibus curantur (from Latin, meaning "like cures like"), a homeopathic axiom introduced by Dr Samuel Hahnemann (1755-1843) in the first edition of his book *The Organon of the Healing Art*.

In conclusion, considering the ease of derivation and ethical aspects, ADSC could indeed be a better source of stem cell (66) than bone marrow-derived stem cells (67). Translated into the topic of present review, this may sound as follows: adipose secretome is better secretome than bone marrow secretome. In brief, the regenerative potential of ADSC's secretome requires further investigation and appreciation.

Altogether, "the mechanisms we have proposed may be incorrect, but they can be tested; if found untenable, they can only be replaced by "better" mechanisms" – Hecther and Halkerston wrote in their 119 page-long chapter (32).

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